TUBERCULOUS INFECTIONS CLASSIFIED FOR AID IN DIAGNOSIS AND TREATMENT.

A. Diagnosis.

I. Non-clinical tuberculosis.
  No symptoms or physical signs.
  May or may not react to tuberculin tests.
II. Clinical tuberculosis.
  With symptoms or physical signs or both.
  Usually react to tuberculin tests.
    (*a*) Masked.
      Physical signs only, no symptoms.
    (*b*) Active.
      Symptoms present.
      Physical signs usually present.
    (*c*) Quiescent or arrested.
      Symptoms present now or formerly.
      Physical signs present or absent.

B. Treatment.

A. Not necessary.
  I. Non-clinical tuberculosis.
  II. Clinical tuberculosis.
    (*a*) Masked.
B. Necessary now or formerly.
  II. Clinical tuberculosis.
    (*b*) Active.
    (*c*) Quiescent or arrested.

IS PERNICIOUS ANEMIA OF INFECTIOUS ORIGIN?[1]

By Herbert C. Moffitt, M.D.,
PROFESSOR OF THE PRINCIPLES AND PRACTICE OF MEDICINE IN THE UNIVERSITY OF CALIFORNIA, SAN FRANCISCO.

Since Addison's description, various types of anemia due to carcinoma, sepsis, parasites, etc., have been differentiated, but there is still left a large group of cases for which the title of cryptogenetic pernicious anemia must be preserved. No matter where seen—in Austria, Switzerland, Germany, Paris, London, Boston, or California—these cases are symptomatically remarkably alike. The difficulties of distinguishing the characteristic blood changes from so-called secondary anemias seem to me much exaggerated. Clinically, the general appearance of the patient, the fever, the cardiovascular, gastro-intestinal, and nervous symptoms, the peculiar remissions, pathologically the pronounced fatty degenerations, the siderosis in liver, spleen, and kidneys, the marrow changes, are as characteristic of the disease as the blood picture. The constancy of these phenomena in practically all cases is in favor of a definite clinical entity, the result of some specific intoxication.

---

[1] Read before the Association of American Physicians, May 10, 1911.

Nearly all authors now agree that the marrow changes are secondary, represent regenerative efforts, and are not in any way specific. Recent investigations have been concerned chiefly with causes of the pathological hemolysis, which is a main feature of the disease. Experimentally by injection of toluylendiamine, ricin, pyridin, saponin, hemolysis may readily be induced and marrow changes and a blood picture may result that closely resemble those of pernicious anemia. Schaumann, Faust, and Tallquist have shown that the anemia due to bothriocephalus is the result of hemolysis produced by a lipoid substance that may be extracted from the segments. In these cases, also, lipoid bodies are to be found in increased amounts in the gastro-intestinal tract. The hemolytic substance isolated by Tallquist was either the sodium or cholesterin combination with oleic acid; normally but little cholesterin was to be found in blood, and when a certain concentration was reached hemolysis occurred. Tallquist suggested therapeutically calcium salts or glycerin to form insoluble or harmless compounds with oleic acid. On the other hand, von Eisler, following the observation of Kruskal that serum inhibited to a certain degree the hemolytic action of saponin, showed that this was due to cholesterin, and Ransome demonstrated that the specific resistance of the erythrocytes was likewise dependent upon cholesterin. In animals, the resistance to saponin hemolysis runs parallel with the cholesterin content of the serum. Morgenroth and Reicher, working with cobra venom and other toxic lecithins, proposed the use of cholesterin therapeutically to inhibit hemolysis. Fejes has recently written of anemia produced experimentally by bacterial hemolysins. Berger and Tsachiya extracted a lipoid substance from the intestinal mucous membrane of individuals dying from pernicious anemia, and found its hemolytic action ten times more potent than extracts from other cases. Anemia of the pernicious type resulted from its injection in animals, a similar lipoid could be obtained from the gastro-intestinal mucous membrane of dogs after production of moderate inflammatory changes. Schlaepfer, employing the method of Ciaccio for preserving lipoids, found lipoid bodies in the intestinal mucous membrane of two cases of pernicious anemia;

in a normal intestine and in a case of secondary anemia they were not obtained. The reports about the various lipoids are, however, still conflicting; other observers have extracted hemolytic substances from the normal intestine, so that we must conclude that no specific toxic body has yet been found.

The recent paper of Grawitz advocates anew the theory of gastro-intestinal intoxication and lays particular stress upon the absence of hydrochloric acid in the stomach as an important factor. But achylia may exist for years without anemia, it is associated not infrequently with intestinal parasites—tenia, uncinariasis, amebiasis—and may result from malignant disease in any part of the body. It is a symptom and not a cause of pernicious anemia. The writer has seen several cases treated by the Grawitz method progress steadily to a fatal issue. Witherspoon has reported a number of cases apparently benefited by measures directed toward the gastro-intestinal tract. In one instance, the symptoms and the character of the stools were influenced favorably by appendicostomy and irrigation. Favorable results have followed the administration of lactic acid preparations. Grawitz would interdict animal albumin in the diet, while Strauss and others advocate overfeeding with meat and peptones. The absence in the majority of cases of signs of intestinal putrefaction, the remarkable appetite and digestion exhibited by many patients, the improvement and apparent cure that may occur without any treatment whatsoever, the persistence of the achylia during remissions—these fact are decidedly against a primary gastro-intestinal intoxication as a cause of the disease. The crises of vomiting and diarrhea not infrequently observed resemble closely the attacks in the course of exophthalmic goitre. Improvement of all symptoms and of the blood picture may follow such a crisis and suggests the elimination of toxic products or the destruction of great numbers of parasites.

Comparatively little has been done in searching for an infectious cause of pernicious anemia. Swiss authors have dwelt upon the occasional endemic occurrence. In the past year, I have seen 7 cases from one of the large interior valleys of California, 3 being from a town of 10,000 inhabitants. Rarely the disease has been observed in two or more members of a family. Of interest in connection with the pernicious anemia of horses, later to be described, is the opinion of some foreign authors that the affection is more commonly met with in country districts. Of 25 cases seen by the author in the past two years, only ten were in city dwellers. The statistics of Cabot, however, by far the best at our command, show that place of residence and condition of life have no influence in etiology.

The theory of buccal or gastro-intestinal infection advanced by Hunter, has been generally abandoned—the sore mouth, not infrequently seen is a symptom and not a cause of the disease. Von

Jacksch, and more recently G. Klemperer have suggested a protozoal origin. Hoefer in a case with recurring fever once, during a period of temperature, observed some peculiar bodies both within and outside the red corpuscles. They resembled piroplasma, but were larger; culture and animal experiments were negative.

Many points of similarity between trypanosomiasis or piroplasmosis and pernicious anemia suggest the possibility of a protozoal infection.

1. Anemia is a prominent feature in many forms of trypanosomiasis and in piroplasmosis—in surra, dourine, caderas, galziekte. In kala azar anemia is usually moderate, but Sheka and Zoypfl have reported the case of a boy, aged nine years, with a count of 2,400,000 red and 1100 to 2000 white cells. In infantile splenic anemia, the result of infection with Leishmania infantum, very low counts have been recorded. In Texas fever in cattle when organisms appear in the peripheral blood, sixty to eighty days after the infecting tick bite, anemia gradually becomes apparent, anisocytosis, poikilocytosis, polychromatophilia, basophilia occur, and normoblasts and megaloblasts later appear. Leukopenia, relative lymphocytosis, and a high color index usually are feature of these protozoal infections.

2. Fever occurs in 79 per cent. of the cases of pernicious anemia (Cabot). Its frequency speaks against a purely toxic cause. It may continue for weeks, may recur periodically, or may be absent during long remissions. Similar peculiarities of the temperature are observed in trypanosomiasis. In certain instances of pernicious anemia, high temperature, profound exhaustion, marked nervous symptoms, and a considerably enlarged spleen speak strongly in favor of a rapidly progressing infection.

3. The remissions of pernicious anemia are among the most remarkable features of the disease; similar remissions are characteristic of a number of protozoal infections. The recurrence of all clinical phenomena of the disease and progression to a fatal issue after remissions of five, ten, fifteen, and even twenty years, make one hesitate to speak of cures in pernicious anemia. Todd, in a recent paper, has emphasized the long periods of apparent freedom in human and animal trypanosomiasis, five and eight years before a final relapse proves fatal.

4. The nervous symptoms and lesions of pernicious anemia, syphilis, and trypanosomiasis are, as Mott and other have pointed out, decidedly similar. But little work has yet been done on the cerebrospinal fluid in cases of pernicious anemia with cord symptoms. In two cases I have found a moderate increase of small mononuclear cells and a positive Nonne, but no Noguchi reaction. These cases, as well as two others without spinal fluid examinations gave a negative Wassermann.

5. From recent investigations, certain lipoid substances seem to play a role in hemolysis in pernicious anemia. Lipoid bodies are likewise increased in syphilis, a spirillosis, and in trypanosomiasis.

6. The only remedies of any value in pernicious anemia are arsenic and arsenical combinations, and arsenical compounds have been found a specific in syphilis and in some forms of trypanosomiasis.

The affection known as equine pernicious or infectious anemia has, of late years, been thoroughly investigated by Carré and Vallée in France, and by Ostertag, in Germany. The first-named authors succeeded in transmitting the disease by inoculation of blood intravenously and subcutaneously and by feeding blood and urine of infected animals. They found the virus potent even after passage through bacterial filters. It is questionable whether the American swamp fever is the same disease. Four years ago, cases of pernicious anemia were noted among horses in one of the interior valleys of Washington, and I am indebted to W. B. Mack, of the University of Nevada, for published reports and recent accounts of cases occurring in eastern Nevada. For fifteen or twenty years, fatalities have been noted among the horses in certain districts, and in 1906 and 1907 the disease became epidemic, causing the death of all horses on some of the ranches. Since 1907, there have been scattered cases. All ages and conditions have been attacked, the disease running an acute, subacute, and chronic course. Few animals recover, though there may be long remissions and apparent cure. The symptoms of subacute and chronic cases are very similar to those of pernicious anemia in man. Irregular high temperatures may persist for weeks or months. Progressive weakness and anemia, throbbing of the vessels of the neck, cardiac insufficiency, dyspnea, edema, paralysis of the hind extremities are the chief symptoms. The appetite is usually ravenous; enlargement of the lymphatic glands may occur. The normal blood count of horses at the altitudes involved in Nevada, about 6000 feet, is given by Mack as considerably over 8,000,000. The lowest count recorded was 2,120,000, with 7300 leukocytes and 38 per cent. hemoglobin. There is always a leukopenia in uncomplicated cases with a relative lymphocytosis—the color index is high. Macrocytosis and nucleated red cells have been observed, but Mack comments upon the fact that the changes in the erythrocytes are not as great as would be expected from the degree of anemia. The disease may be characterized by remissions exactly similar to those that occur in pernicious anemia in man.

Autopsies on fatal cases have shown extensive subserous hemorrhages, fluid in the serous cavities, spleens sometimes normal in size and again considerably enlarged. Extensive megaloblastic metaplasia of the bone marrow has been a constant feature. In two instances, in 1907, Mack succeeded in transmitting the disease to other horses by subcutaneous injection of defibrinated blood from diseased animals. The clinical symptoms, remissions, and autopsy findings were the same as in other cases. His recent experiments have been less positive, and he writes under date of April 19, 1911: "I have been unable to find any microörganism associated with the disease which can be regarded as the causal factor. I have searched diligently for such an organism; bacteria frequently occur in the tissues, but they do not cause the disease; piroplasma or other protozoa have not been found. Some investigators consider the cause a filterable virus, but I have not demonstrated that in my cases; in fact, my inoculations have yielded somewhat conflicting and puzzling results."

During the last year several of my cases have been investigated with the idea of a protozoal origin in mind. Films have been stained or preparations made after the method of Martin and Leboef,[2] centrifugalizing 5 c.c. of blood from a vein to which 1 c.c. of 20 per cent. sodium citrate in normal salt solution has been added. Cultures have been attempted both in normal salt solution recommended by Nuttall and in the 2 per cent. citrate of sodium solution of Rogers, and on the medium advocated by Novy. No bodies resembling protozoa have been found. Inoculations in guinea-pigs have been made, using 2 to 3 c.c. of blood, with negative result. Very few inoculation experiments have been reported in human pernicious anemia. I have in mind in future inoculations of large amounts of blood, of blood from splenic puncture, and of extracts of the tissue at autopsy into dogs, monkeys, and horses. The cases most likely to give positive results are those rather rare ones marked by a rapid progressive course, high temperature, and a greatly enlarged spleen.

THE COAGULATION TIME OF THE BLOOD IN VARIOUS DISEASES.[1]

By R. D. Rudolf, M.D., F.R.C.P.,
PROFESSOR OF THERAPEUTICS, UNIVERSITY OF TORONTO; ASSISTANT PHYSICIAN, TORONTO GENERAL HOSPITAL,

AND

C. E. C. Cole, B.A., M.B.,
DEMONSTRATOR IN THERAPEUTICS, UNIVERSITY OF TORONTO, CANADA.

The method of estimating the coagulation time of the blood, as described by one of us (R. D. R.) last spring before the Association

---

[2] Diagnostic microscopique de la trypanosomiase humaine, Ann. de l'Inst. Pasteur, 25 Juni, 1908, I. xxii, No. 6, pp. 518 to 540.

[1] Read by title before the Association of American Physicians, May 10, 1911.